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Social brains on drugs: tools for neuromodulation in social neuroscience

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Abstract

Neuromodulators such as serotonin, oxytocin, and testosterone play an important role in social behavior. Studies examining the effects of these neuromodulators and others on social cognition and behavior, and their neural underpinnings, are becoming increasingly common. Here, we provide an overview of methodological considerations for those wishing to evaluate or conduct empirical studies of neuromodulation in social neuroscience.

Tools for neuromodulation

Introduction

One of social psychology's most important contributions is the notion that situations are powerful determinants of human behavior (Ross & Nisbett, 1991). Methodological advances in social and affective neuroscience are beginning to provide us with tools for discovering *how*. Brains are sensitive to the surrounding environment, and one mechanism through which environments shape brains is by influencing the function of *neuromodulators*- chemicals that **modify neuronal dynamics, excitability, and synaptic function**. Neuromodulators include neurotransmitters (e.g., serotonin, noradrenaline, acetylcholine, and dopamine) as well as hormones (e.g., testosterone, oxytocin, vasopressin). These chemicals may serve to prepare organisms to interact optimally with the environment, shaping behavior to fit the current context in an adaptive manner. Activation of one or more of these chemical systems is an efficient way to alter the computational properties of neural networks at a global level (Robbins & Arnsten, 2009).

Recent work has begun to examine how manipulating neuromodulators influences social cognitions and behaviors such as trust (Kosfeld, et al., 2005), punishment (Crockett et al., 2013; Crockett et al., 2008), moral judgment (Crockett, et al., 2010a), conformity (Campbell-Meiklejohn et al., 2012; Stallen, et al., 2012), and empathy (Hurlemann et al., 2010). **The effects of specific neuromodulators on social behavior have been reviewed elsewhere (Crockett & Fehr, in press; Siegel & Crockett, in press; Insel, 2010; Eisenegger et al., 2011).** Here, we provide a primer for conducting **and**

Tools for neuromodulation

evaluating empirical studies with neuromodulatory tools, highlighting methodological issues that are particularly salient in the context of studying social behavior. **This topic is important for advancing social, cognitive and affective neuroscience for at least three reasons. First, animal research provides strong evidence that neuromodulators play a crucial role in a range of important social behaviors, including affiliation, aggression, and social dominance (Insel, 2010); neurobiological models of human social behavior will be incomplete without a detailed understanding of neuromodulator effects. Second, the pharmacological techniques used to study neuromodulator function in humans often produce subjective effects on mood and cognitive factors like attention and executive control. As mood, attention and executive control can exert independent influences on social behavior (Lieberman, 2003; Strack & Deutsch, 2004), designing experiments to identify selective effects of neuromodulators on social behavior requires care and consideration. Finally, psychological disorders are often characterized by dysfunctional social cognition as well as abnormal neuromodulator function (Kishida et al., 2010); research examining how neuromodulators influence healthy social cognition may pave the way for pharmacological therapies to ameliorate social disturbances in psychological disorders.**

Methods for manipulating neuromodulators

Direct administration

Tools for neuromodulation

Direct oral or intravenous administration of neuromodulators (e.g., serotonin, norepinephrine and dopamine) is not generally possible, because most of these molecules cannot cross the semi-permeable separation that prevents materials in the bloodstream from entering the brain (called the “blood-brain barrier”). For some neuropeptides (e.g., oxytocin and vasopressin), it may be possible to administer the compounds through the nasal passages, which bypass the blood-brain barrier; **the majority of studies examining how oxytocin affects social behavior have used intranasal administration (Veening & Olivier, 2013)**. However, it remains unclear how intra-nasally administered neuromodulators enter the brain and reach the appropriate receptor sites (Churchland & Winkielman, 2012; Veening & Olivier, 2013). The hormones testosterone and estradiol, which do cross the blood-brain barrier, can be administered orally (**Bos et al., 2011**).

Precursor manipulation

Neuromodulator levels can be influenced by manipulating their chemical precursors, which can be amino acids or other molecules that are able to cross the blood-brain barrier. Neuromodulator **production** can sometimes be enhanced by increasing the availability of precursor via pharmacological or dietary supplementation, or impaired by decreasing the availability of precursor via dietary depletion.

Dietary depletion of precursor results in a reversible, partial global reduction in brain neurotransmitter levels. In the precursor depletion procedure, subjects

Tools for neuromodulation

ingest an amino acid load (usually in liquid or pill form) that does not contain the precursor amino acid but does include other large neutral amino acids (LNAAs). The influx of amino acids lowers the ratio of precursor to other LNAAs. Since the precursor competes with other LNAAs to enter the brain through the blood-brain barrier, lowering the precursor:LNAAs ratio almost completely halts precursor transport into the brain (Booij et al., 2003).

There are two techniques for dietary enhancement of neuromodulator precursors. The first, called *supplementation*, involves administering a smaller dose of the precursor over several days or weeks. The second, called *loading*, involves administering a large acute dose of the precursor. Supplementation and loading are able to enhance neuromodulator production when the enzyme that produces the neuromodulator is not normally saturated. For instance, serotonin production can be enhanced by supplementation or loading of its precursor, the amino acid tryptophan. This is because the rate-limiting enzyme that converts tryptophan to serotonin, tryptophan hydroxylase, is not normally saturated (Silber & Schmitt, 2010).

Further examples of precursor manipulation include tryptophan depletion (impairs serotonin production), tyrosine depletion (impairs noradrenaline and dopamine production), and L-DOPA administration (enhances dopamine production).

Receptor agonists & antagonists

Tools for neuromodulation

Neuromodulators work by binding to different kinds of receptors.

There are many different types of receptors for each neuromodulator system, and different receptor types can have different effects on neuronal function when activated. For example, dopamine D₁ and D₂ receptors can have opposing effects on long-term potentiation and neuronal excitability (reviewed in Frank, 2005). The distribution of different receptor types can vary across the brain; so for instance, D₁ and D₂ receptors are found in roughly equal proportions in the striatum, whereas D₁ receptors outnumber D₂ receptors in much of the prefrontal cortex (Hall et al., 1994). The consequence of this neuronal architecture is that neuromodulators, when released, can have different effects in different brain regions according to the type of receptor activated. Some pharmacological agents directly stimulate or block neuromodulator receptors. These agents can be highly selective (targeting only a specific receptor sub-type) or less so (targeting a general class of receptors and binding to multiple receptor sub-types). *Antagonists* bind to the receptor and block the actions of the endogenous neuromodulator, thus impairing neuromodulator function. *Agonists* bind to the receptor and mimic the actions of the endogenous neuromodulator. When agonists bind to post-synaptic receptors, their net effect is to increase neuromodulator function. However, agonists and antagonists can also influence neuromodulator function by binding to special receptors called *autoreceptors*. Autoreceptors are located on the **neurons** that produce and release neurotransmitters. When activated, autoreceptors inhibit synthesis and release of neurotransmitter. This is a negative feedback

Tools for neuromodulation

mechanism designed to keep neurotransmitter release in homeostatic balance. Meanwhile, antagonism of autoreceptors can stimulate neurotransmitter synthesis and release by blocking negative feedback brought on by endogenous neurotransmitter. Thus, when they bind to autoreceptors, agonists have the net effect of decreasing neuromodulator function, while antagonists have the net effect of increasing neuromodulator function. The effects of agonists and antagonists on neuromodulator function therefore depend on whether they activate pre-synaptic or post-synaptic receptors. Examples of such drugs include haloperidol (antagonist for multiple dopamine receptors), sulpiride (antagonist for dopamine D₂ receptors), pramipexole (agonist for dopamine D₂ receptors), bromocriptine (agonist for dopamine D₁ and D₂ receptors), and propranolol (antagonist for noradrenaline beta receptors).

Re-uptake inhibition

Selective re-uptake inhibitors increase the concentration of neuromodulator in the synapse by blocking its presynaptic re-uptake. Re-uptake inhibitors work by blocking the presynaptic active transport mechanism in the transporter protein, located on the cell membrane, that is responsible for taking up neurotransmitter from the synapse after its release. Consequently, the action of the neuromodulator on postsynaptic receptors is prolonged. Examples of re-uptake inhibitors include citalopram, paroxetine and fluoxetine (selective serotonin re-uptake inhibitors, or SSRIs); atomoxetine and reboxetine (selective noradrenaline re-uptake inhibitors, or SNRIs); and methylphenidate (a dopamine

Tools for neuromodulation

re-uptake inhibitor).

There is some evidence that acute administration of re-uptake inhibitors can under certain conditions lead to a net decrease in the release of neuromodulator. This is thought to be caused by the down-regulating effects of pre-synaptic autoreceptor activation. For instance, a recent study showed that a 10mg intravenous dose of citalopram led to a net decrease in endogenous serotonin release by the raphé nuclei, brought on by enhanced serotonergic transmission within the raphé nuclei (Selvaraj et al., 2012). Studies in animals suggest that the dosage used is likely to influence whether acute SSRI administration enhances or reduces 5-HT neurotransmission, with lower doses reducing 5-HT neurotransmission (via autoreceptor negative feedback) and higher doses enhancing 5-HT neurotransmission (Bari et al., 2010). However, further research is needed to specify the effects of reuptake-inhibitor dosages on neurotransmission in human subjects.

Metabolic enzyme inhibitors

The synaptic actions of neurotransmitters can be prolonged by pharmacologically restraining the metabolic enzymes that break down neurotransmitters after they're released. One example is galantamine, which inhibits the enzyme that degrades acetylcholine, thus prolonging cholinergic actions in the brain.

Tools for neuromodulation

Practical issues in behavioral psychopharmacology

Placebo and blinding issues

One advantage of using pharmacological manipulations to study the neurobiology of social behavior is that such manipulations can establish *causal* mechanisms, as long as the experiment is properly designed. Perhaps the most important feature of pharmacological experiment is the *double-blind placebo control*. In the experimental condition, participants receive the pharmacological agent; in the control condition, participants receive an inactive placebo. All aspects of the experimental procedure are identical aside from the administration of drug vs. placebo. Critically, neither the experimenter nor the participants know whether they have received drug or placebo. On the experimenter side, this is important so that the experimenter does not bias the data collection process, either consciously or unconsciously. On the participant side, this is important because beliefs about whether one has received drug or placebo can influence behavior independently from the effects of the drug itself (Eisenegger et al., 2009).

Maintaining double-blind conditions can be difficult, however, when the pharmacological agent induces physical side effects such as nausea, increased heart rate, or dizziness, all of which are common symptoms of drugs typically used to manipulate neuromodulators, even at relatively low doses. Note that side-effects can be more severe in a neuroimaging environment. **In addition to potentially interfering with task performance and producing subjective mood effects that could independently affect the dependent measures of**

Tools for neuromodulation

interest, side-effects also make it more likely that subjects will be able to distinguish between the drug and placebo.

One approach to this issue is to employ a *positive control* -- a second pharmacological agent used as a comparison condition for the drug of interest that has a similar side effect profile. For example, if one is interested in studying how serotonin influences social behavior, one could compare the effects of citalopram (a serotonin reuptake inhibitor) with those of atomoxetine (a noradrenaline reuptake inhibitor with a similar side effect profile to citalopram) as well as placebo (Crockett et al., 2010a). With this procedure, even if participants can distinguish between drug and placebo due to physical side effects, as long as they cannot distinguish between the experimental treatment (e.g., citalopram) and the positive control (e.g., atomoxetine), some degree of blindness can be maintained. Using a positive control has the additional benefit of probing for the neurochemical selectivity of the effect of interest in terms of the neuromodulator systems involved in the process under examination.

Controlling for beliefs

Even when one goes to great lengths to set up a double-blind placebo-controlled procedure, participants may nevertheless form beliefs about which treatment they received that can significantly affect their behavior. It is therefore important to ask participants to report, at the end of the experiment, their subjective beliefs about which treatment they received. This belief data can be important: a notable example comes from a recent study examining the effects of

Tools for neuromodulation

testosterone on bargaining behavior (Eisenegger et al., 2009). While testosterone caused participants to make more generous offers during a bargaining game, those subjects who believed they had received testosterone (as reported in the post-experiment questionnaire) made *less* generous offers, regardless of whether they actually received testosterone or placebo. The authors hypothesized that this belief effect reflects folk wisdom about testosterone: namely, that it causes antisocial or aggressive behavior. Thus, participants who believed they received testosterone may have felt 'morally licensed' to make less generous offers. This finding underscores the importance of measuring beliefs in these kinds of experiments, particularly when studying complex social interactions where beliefs can play a decisive role.

Between-subjects versus within-subjects designs

In pharmacological studies, the drug treatment can be carried out either *between subjects* (in which one group of participants receives the pharmacological agent, and another matched group of participants receives placebo) or *within subjects* (in which participants take part in the experiment in multiple sessions, receiving placebo in one session and the drugs in the other sessions, with the order of treatments counterbalanced across participants). Each approach has advantages and disadvantages. Within-subjects designs tend to be more powerful statistically: because each participant serves as her own comparison, error variance associated with individual differences is reduced. This is particularly important in pharmacological experiments, because there are

Tools for neuromodulation

several known genetic polymorphisms that influence the signaling properties within neuromodulator systems (e.g., the function of specific types of neuromodulator receptors). These polymorphisms could create potentially large variation between individuals in terms of their physiological response to pharmacological treatment.

Within-subjects designs are less desirable when the behavior under study is susceptible to learning/practice effects or change across time, since subjects participate in the experiment multiple times. For example, Wood et al. (2006) used a within-subjects design to examine the effects of tryptophan depletion on behavior in a repeated prisoner's dilemma, in which two players learn about each other's propensity to cooperate or defect. Tryptophan depletion reduced cooperative behavior, but only on the first experimental session, i.e., when participants were naïve to the prisoner's dilemma task and early in the process of learning about the strategy of the other player. On the second experimental session, (after subjects had already learned the other player's strategy), tryptophan depletion had little effect (Wood et al., 2006).

In addition, some social psychological paradigms are difficult (if not impossible) to conduct in a repeated-measures setting. In particular, those paradigms that involve deception pose a challenge for repeated-measures designs. Generally, when the research paradigm requires convincing subjects of something that is not true (e.g., subjects are led to believe that they are interacting with a real person, when in fact they are interacting

Tools for neuromodulation

with a computer program), it is advisable to collect self-report measures at the end of the study to assess whether the subject believed the experimenter's cover story. However, in a repeated-measures design, collecting self-report measures of belief in the cover story at the end of the first experimental session may contaminate behavior in the second experimental session, if the self-report measures raise suspicions about the veracity of the cover story where none were present before. To avoid this possibility, one might only collect belief measures at the end of the second session; however, this approach rests somewhat on the assumption that subjects' beliefs about the veracity of the cover story are consistent across sessions and treatments, which may not be the case (see below, section 'Demonstrating behavioral selectivity').

If the aim of the experiment is to examine neuromodulator effects on learning or one-shot decisions, or in paradigms where within-subjects treatments are infeasible, a between-subjects design may be more appropriate. When using a between-subjects design, it is critical to ensure that the experimental group and the placebo group are matched on important characteristics such as sex, age, education, and perhaps also personality traits and genetic polymorphisms relevant to the neuromodulator system under study. While a detailed review of the effects of genetic polymorphisms beyond the scope of this review, it is worth mentioning that the effects of pharmacological manipulations can vary according to genotype (Eisenegger et al., 2010; Rogers, 2010), an issue worth considering when designing pharmacological experiments,

Tools for neuromodulation

especially those with between-subjects designs.

Timing of drug administration

The time course of the effects of pharmacological manipulations varies depending on the agent used and the method of administration. Following oral administration of drugs, peak concentrations tend to occur within a few hours, while intravenous and intranasal administration tend to have faster-acting effects. Meanwhile, dietary depletions take considerably longer to exert their effects, on the order of 5-6 hours. It is important to precisely time the experimental procedure such that the dependent measures are collected at the time point most likely to coincide with peak drug effects.

If more than one pharmacological agent is used, and the drugs have different time-courses, a multiple-placebo procedure can be employed to maintain double-blind conditions. For example, consider a study comparing the effects of levodopa and citalopram with placebo, where levodopa reaches peak concentration 1 hour after administration, and citalopram reaches peak concentration 3 hours after administration. The levodopa group receives levodopa 1 hour prior to testing, and a placebo pill 3 hours prior to testing. The citalopram group receives placebo 1 hour prior to testing, and citalopram 3 hours prior to testing. Finally, the placebo group receives placebo at both 1 and 3 hours prior to testing. Thus, across conditions all subjects receive treatment at both 1hr and 3hr pretesting, but neither the subjects nor the experimenters know the contents of the treatment, maintaining double-blind conditions.

Tools for neuromodulation

Another consideration related to timing relates to experiments using within-subjects designs. Drugs differ in the amount of time they take to leave the body. In within-subjects designs, it is important that testing sessions are spaced sufficiently far apart for a full washout to occur, generally at least one week. When recruiting subjects, it is also worth checking whether they have recently participated in other studies involving pharmacological manipulations. In addition, since other substances such as alcohol, caffeine, and recreational drugs can have prolonged effects in the brain and can interact with your experimental treatment, it is important to make sure subjects abstain from these substances for at least 24 hours prior to participation, and throughout the duration of the study (for within-subjects designs).

Finally, if females are included in the study, it is worth considering whether to control for menstrual phase cycle, since endogenous sex hormones could potentially interact with the neuromodulator under study. If this is a concern, it is good practice to restrict female participants to those with a regular menstrual cycle who are not taking oral contraceptives, and to test them in the early follicular phase of the cycle, when the endogenous level of sex hormones tends to be low and stable.

Choosing the appropriate dose

The chosen dose of the drug can have important implications for the effects of the manipulation. For example, low doses of sulpiride (a D2 antagonist; e.g., 100-200mg) are thought to primarily exert effects on pre-synaptic receptors,

Tools for neuromodulation

potentially leading to a net stimulatory effect on DA neurotransmission, while higher doses (e.g., 400-800mg) are more likely to act post-synaptically and reduce DA actions on D2 receptors (Di Giovanni et al., 1998). Meanwhile, low doses of SSRIs (e.g., 10mg) can reduce serotonin release by enhancing the actions of endogenous serotonin on pre-synaptic autoreceptors (Selvaraj et al., 2012), whereas higher doses (e.g., 30mg and above) may be sufficient to enhance serotonin neurotransmission in terminal regions. In line with this idea, studies in animals have shown that different doses of SSRIs have different effects on motivated behavior (Bari et al., 2010). In humans, the effects of pharmacological manipulations at the molecular level are incompletely understood and should be interpreted with caution. Future studies combining pharmacological manipulations with positron emission tomography (PET) are needed to elucidate the effects of these manipulations on endogenous neurotransmitter synthesis and release.

Blood plasma measures

As noted previously, there are widespread individual differences in physiological responses to pharmacological treatments. Collecting additional data from blood samples can provide information about the nature of these individual differences, and how they interact with the treatment.

When conducting precursor **depletion** studies, it is essential to collect blood samples both at baseline (i.e., before ingesting the amino acids) and just before testing. This enables confirmation that plasma levels of precursor, and the ratio

Tools for neuromodulation

of precursor to LNAAs, were indeed **depleted** by the manipulation (Booij et al., 2003), **because the procedure can be compromised by participant non-compliance (e.g., if the participant consumes any foods containing the precursor during the waiting period)**. Individual differences in plasma precursor levels can also serve as covariates in behavioral and neuroimaging analyses. For instance, individual differences in plasma tryptophan:LNAAs ratios predicted individual differences in the effects of tryptophan depletion on impulsive choice behavior (Crockett et al., 2010b), and subject-specific plasma tryptophan:LNAAs ratios influenced reward prediction error responses in the putamen (Seymour et al., 2012).

Unlike precursor depletion studies, drug or precursor administration studies do not necessarily require measurement of plasma levels of the drug, since these procedures are less vulnerable to participant non-compliance. However, it can still be useful to collect blood samples to measure plasma levels of the drug, which sometimes covary with the drug's behavioral and/or neural effects. For example, Chamberlain et al. (2009) found that plasma levels of atomoxetine predicted right inferior frontal gyrus activity during response inhibition (Chamberlain et al., 2009).

Note that for substances that cross the blood-brain barrier (e.g., tryptophan or atomoxetine), plasma levels of the substance are likely correlated with brain levels of that substance. However, for substances that have low penetration of the blood-brain barrier (e.g., oxytocin or vasopressin), plasma levels are not necessarily indicative of brain levels of that substance. Studies that use plasma

Tools for neuromodulation

levels of a substance with weak penetration of the blood-brain barrier to make claims about brain levels of that substance should therefore be interpreted with caution (Churchland & Winkielman, 2012).

Controlling for subjective experience

Because pharmacological manipulations can have physical side effects or influence mood more generally, it is important to rule out these factors as causal mediating forces in the effects of neuromodulators on social behavior. Subjective rating scales are a useful tool for assessing these effects. Commonly used scales include the Visual Analogue Scales (Bond & Lader, 1974) and the Positive and Negative Affect Scales (Watson et al., 1988). These scales assess the effects of the pharmacological manipulation on subjective feelings such as alertness, calmness, irritability, contentedness, drowsiness, anxiety, nausea, dizziness, and positive and negative affect. Drug-induced changes in physical side effects or mood can be included as regressors of no interest in statistical models capturing the effects of pharmacological manipulations on social behavior.

Demonstrating behavioral selectivity

It is relatively straightforward to pick some behavior Z and perform a pharmacological study to examine the effects of neuromodulator X on behavior Z . However, to make the claim that X has a *selective effect* on Z requires some methodological sophistication. Because social behaviors are complex constructs

Tools for neuromodulation

incorporating several more basic perceptual and motivational processes (many of which may be sensitive to the neuromodulator in question), to make claims about neuromodulators' behavioral selectivity, one must control for these basic processes where possible.

An example of this comes from a study on how oxytocin affects behavior in a game of trust. In this study, oxytocin increased subjects' trusting behavior by 17%, relative to a placebo control group (Kosfeld et al., 2005). But before the authors could conclude that oxytocin modulates trust specifically, they had to rule out the possibility that oxytocin simply altered sensitivity to risk, as trust involves a degree of risk-taking. To do this, they conducted a risk experiment, in which subjects faced exactly the same decisions as in the trust game, but removed from a social context: the interaction partner was replaced with a computer. Critically, oxytocin did *not* affect behavior in the risk experiment, indicating that the effects of oxytocin on trust are specific to the social context.

Another issue worth considering is the possibility that neuromodulators may influence susceptibility to deception and/or experimenter demand effects. Oxytocin, for example, enhances trust in some settings (Van IJzendoorn & Bakermans-Kranenburg, 2012) and there is no a priori reason to assume that these effects do not extend to trust in the experimenter. Thus, paradigms in which experimenter demand effects are expected to be high, and/or those involving deception of subjects by the experimenters, may show an effect of oxytocin on the behavior of interest not because oxytocin actually influences the behavior of interest,

Tools for neuromodulation

but because it enhances trust in the experimenter, and consequently, subjects' engagement with the task. It is therefore critical to collect, where possible, independent measures of subjects' beliefs about the veracity of the experimental set-up, engagement with the task, and desire to please the experimenter, in order to control for possible neuromodulator effects on these measures.

Conclusion

One important challenge for human psychopharmacology is the scarcity of methods for assessing the molecular-level effects of pharmacological manipulations *in vivo*. While it is straightforward to investigate how drug treatments alter behavior and brain hemodynamic responses, these measures reflect downstream effects of the changes in neurotransmission at the molecular level. Previous pharmacological studies in humans provide evidence of behavioral effects, but can say very little about the underlying changes in neurotransmission. Positron emission tomography (PET) imaging can provide quantitative measurements of endogenous neurotransmitter release (Martinez et al., 2003; Selvaraj et al., 2012); future studies could combine pharmacological manipulations with PET, fMRI and behavioral measurements to link the drug treatment to changes in endogenous neurotransmitter release to changes in neural activity to changes in behavior.

As social neuroscience progresses, it will become ever more important to employ methods that enable inferences about cause and effect. The combination

Tools for neuromodulation of pharmacological manipulations with neuroimaging will facilitate the identification of the brain networks that are causally involved in generating social cognition and behavior. These kinds of studies will bring us closer to a mechanistic understanding of social interaction.

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Tools for neuromodulation

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